REMARKS

Status of the Claims

Claims 38-45 and 113-121 are pending in the present application. Claims 1-37 and 46-112 have been cancelled without prejudice to or disclaimer of the subject matter contained therein due to the restriction requirement. Applicants expressly reserve the right to file additional applications directed to the cancelled subject matter. Also in response to the restriction requirement, claim 42 has been amended to omit the reference to SEQ ID NO:8. New claims 113-121 have been added. New claim 113 is directed to the subject matter deleted from original claim 42, and has been added for consideration at such time as generic claim 38 is found to be patentable. Claims 38-40 and 44 have been amended to correct informalities noted by the Examiner. Claim 38 has also been amended to recite that the A-subunit of the expanded binding pocket is increased by about 58 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3, and the pocket volume of the B-subunit of the expanded binding pocket is increased by about 138 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3. The amendments to the claims and the new claims are supported by the original claims and specification. No new matter is added by way of amendment. Reconsideration and withdrawal of the rejections are respectfully requested.

The Restriction Requirement

Applicants acknowledge the election with traverse of Group V, and the selection of SEQ ID NO:6 for prosecution in claim 42. Prior to the present amendment, claim 42 recited two species, SEQ ID NO:6, and SEQ ID NO:8, which are embraced by generic claim 38. Applicants have amended claim 42 to remove the reference to the non-elected sequence SEQ ID NO:8, and have added new claim 113, which is directed to the subject matter deleted from original claim 42. Claims 42 and 113 are linked by independent claim 38, and are fully embraced by this claim. Accordingly, at such time that generic claim 38 is found to be allowable,

the subject matter of claim 113 should no longer be withdrawn from consideration pursuant to MPEP § 809.02(c), and should be considered on the merits at that time.

The Objection to the Specification

The Examiner has objected to the specification on the grounds that it contains hyperlinks. The specification has been amended to remove the hyperlinks, thereby obviating the rejection.

The title has been objected to on the grounds that it is not descriptive of the claims elected for prosecution in the present application. The title has been amended to more clearly describe the elected subject matter, thereby obviating the objection.

The specification has been objected to on the grounds that Figure 17 contains sequences that are not included in the sequence listing. A new sequence listing which includes the sequences shown in Figure 17 has been prepared and accompanies the present response. In addition, the description of Figure 17 has been amended to refer to the SEQ ID NO corresponding to each sequence. Accordingly, the objection has been obviated.

The Objections to the Claims

Claims 38 and 40 have been objected to by the Examiner on the grounds that they contain certain informalities. These claims have been amended as suggested by the Examiner to correct these informalities. Specifically, claim 38 has been amended to clarify that by "GR" it is intended "glucocorticoid receptor" and claim 42 has been amended to clarify that by "TIF2" is intended "transcription intermediary factor 2." Accordingly, the objection to the claims has been obviated.

Claim 40 has been objected to on the grounds that it contains an error in antecedent basis. Claim 40 has been amended to correct this error, thereby obviating the objection.

Claim 42 has been objected to on the grounds that it contains non-elected subject matter. Claim 42 has been amended to delete this subject matter, thereby obviating the rejection. New claim 113 is directed to the subject matter deleted from original claim 42, so that this subject matter may be considered upon a finding that generic claim 38 is allowable.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 38 and dependent claims 39-45 have been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the phrase "expanded binding pocket" is indefinite. Applicants respectfully disagree with the rejection. The *Manual of Patenting Examining Procedure* (*MPEP*) states that "[t]he test for definiteness under 35 U.S.C. 112, second paragraph is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.'" *MPEP* (8th ed.) § 2173.02, citing *Orthokinetics, Inc. v. Safety Travel Chairs, Incl,* 805 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). Claim 38 meets this requirement because the specification provides a description of the GR expanded binding pocket. See, for example, lines 7-17 of page 31 of the specification. Accordingly, one of skill in the art, when reading claim 38 in light of the supporting specification, would understand what is encompassed by the claim. Nevertheless, in order to expedite prosecution, claim 38 has been amended to recite that the A-subunit of the expanded binding pocket is increased by about 58 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3, and the pocket volume of the B-subunit of the expanded binding pocket is increased by about 138 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3. Support for the amendment may be found in the specification as filed including, for example, on lines 9-15 of page 31. The amendment obviates the rejection under 35 U.S.C. § 112, second paragraph.

Claims 38 and 39 have been rejected under 35 U.S.C. §112, second paragraph, on the grounds that these claims are inconsistent in the way that they refer to "a GR polypeptide complex." Applicant acknowledges the inconsistency noted by the Examiner, and has amended claims 38 and 39 to correct this error. Specifically, claim 38 has been amended to recite a "GR polypeptide", and claim 39 has been amended to recite that the GR polypeptide is comprised within a GR

polypeptide complex which further comprises a co-activator and fluticasone propionate. Accordingly, the amendment obviates the rejection.

Claim 43 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that it is indefinite because there is not antecedent basis for the term "ligand." Applicants respectfully traverse the rejection. Claim 43 depends from claim 38, and part (b) of claim 38 recites the step of modeling a ligand. Accordingly, the term "ligand" in claim 43 has antecedent basis in claim 38.

Claim 44 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that it is unclear what atomic coordinates are intended to be encompassed by the claim. Applicants have amended claim 44 to recite that the atomic coordinates are those shown in Table 2. This amendment obviates the rejection.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. § 112, second paragraph, have been obviated or overcome. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

The Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 38-45 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that these claims do not comply with the written description requirement. The rejection is respectfully traversed as applied to the amended claims for the reasons described below.

The *MPEP* states:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

MPEP (8th ed.) § 2163, citing *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002). Claims 38-45 meet this requirement, because these claims specifically recite the structural characteristics which identify the GR polypeptide structures that are encompassed by the claimed methods.

Claim 38 as amended is directed to a method of identifying GR modulators, where the method comprises the step of providing the atomic coordinates of a GR polypeptide structure comprising an expanded binding pocket to a computerized modeling system, where the A-subunit of the expanded binding pocket is increased by about 58 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3, and the pocket volume of the B-subunit of the expanded binding pocket is increased by about 138 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3. The specification provides additional description of the structural features of the expanded binding pocket. Accordingly, the specification provides sufficient detailed, relevant, identifying characteristics to describe the GR polypeptide structures encompassed by the claim and demonstrate that the applicants were in possession of the claimed invention. Accordingly, the written description requirement under 35 U.S.C. § 112, first paragraph, is met.

Claims 38-45 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the claimed invention does not provide sufficient enablement to allow one of skill in the art to make and use the claimed invention. The rejection is respectfully traversed for the reasons described below.

In order to meet the enablement requirement, the disclosure must describe the claimed invention in such a way as to enable the ordinarily skilled artisan to make and use the invention, and this description must be commensurate with the scope of the claimed invention. The test for sufficient enablement is not whether experimentation is required to make and use the invention, but rather if experimentation is required, whether it is undue. *In re Angstadt*, 537 F.2d 489, 498, 190 USPQ 214, 219 (C.C.P.A. 1976). The Federal Circuit has held that a number of factors must be considered in order to determine whether undue experimentation would be required to practice an invention. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors include the breadth of the claimed invention, the amount of guidance provided in the specification, the presence of working examples of the invention in the application, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability in the art, and the quantity of experimentation necessary. *Id.*

In the present case, consideration of the *Wands* factors demonstrates the applicants have provided sufficient guidance to allow one of skill in the art to practice the methods recited in claims 38-45 and 113-121. The claims are directed to methods of identifying GR modulators, where the method comprises the steps of providing atomic coordinates of a GR polypeptide structure comprising an expanded binding pocket to a computerized modeling system, and modeling a ligand that fits spatially into the large pocket volume of the polypeptide structure to thereby identify a GR modulator. Claim 38, from which claims 39-45 and 113-121 depend, further states that the pocket volume of the A-subunit of the expanded binding pocket of the GR polypeptide is increased by about 58 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3, and the pocket volume of the B-subunit of said expanded binding pocket is increased by about 138 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3. Accordingly, the claimed methods are directed to identifying GR modulators by computerized modeling of GR polypeptide structures having an expanded binding pocket with well-defined structural features.

In addition, the specification provides extensive guidance for practicing the claimed methods. The specification provides the structure of the crystal structure of a GR polypeptide complex having an expanded binding pocket (see, for example, Table 2 and Figures 6A, 6B, 7A, 7B, 8A, 8B, 9, 10, 11, 12, 13, 14, 15, and 16), and describes the features that distinguish this structure from GR polypeptide complexes that do not have an expanded binding pocket. See, for example, lines 14-24 of page 30 and lines 4 of page 31 through line 22 of page 34 of the specification. The specification also provides guidance for analyzing other nuclear receptors to identify homologous residues involved in creating an expanded binding pocket. See, for example, line 25 of page 30 through line 3 of page 31.

Examples of GR polypeptide complexes that may be used in the claimed methods are given on line 22 of page 33 through line 22 of page 34. Guidance regarding the regions of the GR polypeptide involved in binding coactivator is provided, for example, on line 10 of page 55 through line 11 of page 56. Examples

of coactivators and ligands that can form a complex with the GR polypeptide are described, for example, on line 29 of page 56 through line 21 of page 58.

Methods of using of the structure of the GR polypeptide expanded binding pocket to assist in designing new modulators of GR that fit spatially into the GR large pocket volume are described, for example, on line 4 of page 73 through line 2 of page 87. Methods of using the GR/FP structure to design homology models of related nuclear receptors, including other GR's, are described, for example, on line 3 of page 87 through line 6 of page 93. Guidance regarding methods of modeling the interaction between a nuclear receptor and a ligand is provided, for example, on line 8 of page 93 through line 33 of page 96. Methods of using the GR/FP structure to solve the structure of related nuclear receptors using a molecular replacement approach are described on line 24 of page 125 through line 28 of page 126. In summary, the inventors have provided detailed and comprehensive guidance regarding the steps that are required to practice the methods recited in claims 38-45 and 113-121.

The enablement of the present invention is also demonstrated by working examples. The inventors have provided the atomic coordinates of a GR polypeptide structure having an expanded binding pocket as recited in claim 38. The atomic coordinates were obtained by solving the crystal structure of GR in a complex with FP. The inventors have also used the structure of the GR expanded binding pocket to model the binding of two additional ligands, benzoxazin-1-one and A-222977. See, for example, line 3 of page 86 through line 2 of page 87 and Examples 6 and 9. Thus, the specification provides multiple working examples of the methods recited in claims 38-45 and 113-121. These examples demonstrate that the claimed methods may be practiced by one of ordinary skill in the art without undue experimentation

The Office Action states that the atomic coordinates of GR ligand complexes were described in the prior art, but that it is unlikely that these coordinates represent all GR protein complexes. Applicants note that the limitations of the prior art structure are precisely what the present invention is intended to address. While the prior art provided the structure of some GR/ligand complexes, the prior art did not teach or suggest the structural requirements for the association of larger ligands such as FP with nuclear receptors. The present invention is directed at identifying the structural features that govern such interactions, and the inventors have

demonstrated that nuclear receptors such as GR form an expanded binding pocket when they bind to larger ligands such as FP. The claims are directed to the use of this newly-identified ligand-binding structure in identifying new GR modulators.

In conclusion, when all of the *Wands* factors are considered together, it is clear that undue experimentation would not be required to practice the methods of claims 38-45 and 113-121 in view of the breadth of the claims (which are directed to methods of identifying GR modulators using a GR polypeptide structure having an expanded binding pocket), the amount of direction provided in the specification (which provides extensive guidance for practicing the methods), the presence of multiple working examples, the prior art (which teaches methods for designing and modeling ligands based on the three-dimensional structure of the ligand binding site), and the high level of skill of those in the art. These factors all favor a conclusion that one of skill in the art could practice the claimed invention without undue experimentation, and that claims 38-45 and 113-121 meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. § 112, first paragraph, have been overcome or obviated. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C. § 102

Claims 38 and 45 have been rejected under 35 U.S.C. §102 on the grounds that these claims are anticipated by WO0052050 (Gilner *et al.*). In addition, claims 38 and 42-45 have been rejected on the grounds that they are anticipated by WO03/015692 (Apolito *et al.*). The rejections are respectfully traversed for the reasons described below.

Claim 38 as amended recites the step of providing atomic coordinates of a GR polypeptide structure comprising an expanded binding pocket to a computerized modeling system, where the pocket volume of the A-subunit of said expanded binding pocket is increased by about 58 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3, and the pocket volume of the B-subunit of said expanded

binding pocket is increased by about 138 cubic angstroms in comparison with the corresponding subunit of the GR/dexamethasone structure having the coordinates set forth in Table 3. Neither Gilner *et al.* nor Apolito *et al* teach a GR polypeptide structure having an expanded binding pocket. Accordingly, these references do not anticipate claim 38 or dependent claims 42-45.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. § 102, have been overcome or obviated. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C. § 103

Claims 39-41 have been rejected on the grounds that they are obvious over WO03015692 (Apolito *et al.*) in view of Johnson (1998) *J. Allergy Clin. Immunol.* 101:S4343-9 and Högger *et al.* (1994) *Steroids* 59:597-602. The rejection is respectfully traversed for the reasons described below.

One of the three key criteria required to establish a *prima facie* case of obviousness is that the cited prior art reference or references teach or suggest all of the claim limitations. *Manual of Patent Examining Procedure* (8th ed.) § 2142, citing *In re Vaeck*, 947 F.2d 488, 200 USPQ2d 1438 (Fed. Cir. 1991). The cited references do not meet this requirement. Claim 38, from which claims 39-41 depend, is directed to a method of identifying a GR modulator, where the method comprises the step of providing atomic coordinates of a GR polypeptide structure comprising an *expanded binding pocket* to a computerized modeling system. None of the cited references, either alone or in combination, teach or suggest the use of a GR polypeptide having an expanded binding pocket.

Apolito *et al.* teach the structure of GR in complex with dexamethasone (GR/dex). However fluticasone propionate (FP) is a larger GR ligand than dexamethasone, and it binds to GR with higher affinity than dexamethasone does. As a result, the GR/dex structure described by Apolito *et al.* does not teach the structural requirements for the association of larger ligands such as FP with GR (see, for example, lines 7-9 of page 9 of the specification). In addition, the GR/dex structure does not provide an answer to the question of why GR has a higher affinity for fluticasone propionate (FP) than for dexamethasone (see, for example, lines 5-7

of page 9 of the specification). It is the present disclosure, which describes the expanded binding pocket of GR when it is complexed with FP, that provides the first insight into the structural requirements for the interaction of nuclear receptors with larger ligands such as FP. None of the cited references, either alone or in combination, teach or suggest a GR polypeptide structure having the structural features recited in the claims. Accordingly, the references do not support a *prima facie* case of obviousness, and claims 38-45 and 113-121 are patentable over these references.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 103, have been overcome. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

It is believed that the current application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, an interview would expedite prosecution, the Examiner is invited to call the undersigned.

Applicants believe that no fees are due in connection with the filing of this paper other than those specifically authorized herein. However, should any other fees be deemed necessary to effect the timely filing of this paper the Commissioner is hereby authorized to charge such fees to Deposit Account No. 07-1392.

Respectfully submitted,

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